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In re Application of: Michael F. Murray Art Group: 1617
Serial No.: 09/609,552 Examiner: Russell Travers, J.D., PhD
Filed: 6/30/2000
For: Treatment of Retrovirus Induced Derangements with Niacin Compounds
Atty. Docket No.: PHJM0609-001

#16
7/8/03

DECLARATION OF MICHAEL F. MURRAY, M.D.

I hereby declare that:

1. I am the named inventor of United States patent application serial number 09/609,552 (the "'552 application"). A copy of the '552 application is attached as **Exhibit A**.

Experience/Expertise of Declarant

2. I am a licensed physician.

3. I am a board certified specialist in infectious diseases.

4. I have been practicing medicine since receiving my medical degree in 1988.

5. I have been treating patients with retroviral infections on a regular basis since 1991.

Applicability of '552 application to patients in need of increase in systemic tryptophan

6. While there is a correlation between retroviral infection and tryptophan depletion there is significant interpatient variability. Thus, not every patient infected with a retrovirus will necessarily require the intervention suggested by the invention disclosed in the '552 application. The invention disclosed in the '552 application will specifically benefit patients in need of therapy to maintain or increase their systemic tryptophan levels.

Long-Felt Need

7. The infectious disease community has noted, evaluated and discussed that tryptophan depletion can often be associated with patients infected with a retrovirus. For example, attached as **Exhibit B** are eight articles that examine various aspects of plasma or serum tryptophan in HIV infected patients (referred to as the "eight articles"). Also included as part of **Exhibit B** is a summary that I prepared of the eight articles. The eight articles of **Exhibit B** are not exhaustive of all articles published, but examples of the types of articles that can be found in published medical literature.

8. The infectious disease community has been aware of the possibility of tryptophan depletion occurring in patients with HIV since at least as early as 1988. *See, e.g.*, **Exhibit B**. Nowhere do the eight articles suggest the administration of niacin to restore tryptophan levels. *See* **Exhibit B**. Similarly, none of the many articles by other authors that I have

reviewed have ever suggested the administration of niacin to restore tryptophan levels.

Skepticism of Experts in June of 2000

9. At the time the '552 application was filed on June 30, 2000, not only was the infectious disease community not considering the use of niacin to treat tryptophan depletion, the infectious disease community was skeptical of whether niacin had a place at all in the treatment of a patient infected with a retrovirus.

10. For example, I prepared a manuscript titled "Niacin as a Potential AIDS Preventative Factor" (referred to as "my Niacin Hypothesis"), a true and correct copy of which is attached as **Exhibit C**. My Niacin Hypothesis was ultimately published in the journal *Medical Hypotheses* in November of 1999. *Medical Hypotheses* is a journal that publishes manuscripts on any topic within the broad scope of the biomedical sciences following a limited editorial review, but without expert based peer review.

11. In my Niacin Hypothesis, I hypothesized that HIV infection that therapeutic niacin would act as an AIDS preventative factor. Prior to the filing of the '552 application, there was no published or publicly presented data that supported my hypotheses for treating retrovirally infected patients with niacin or that suggested that niacin therapy had any measurable benefit. In fact, a study by Skurnick et al suggested that retrovirally infected patients had increased levels of niacin in their blood steam, thereby inferring that additional treatment of patients with a compound that they had in excess would be of no obvious value. *See* **Exhibit G**, Skurnick, et al. Micronutrient Profiles in HIV-1 Infected Heterosexual Adults, at 80.

12. In a study based on my hypothesis, however, I discovered that the administration of a daily dose of niacin in patients already receiving adequate dietary intakes of both tryptophan and niacin increased levels of systemic tryptophan. See **Exhibit A**.

13. As demonstrated in the following paragraphs, my Niacin Hypothesis regarding the use of niacin as an AIDS preventative factor was not well received by the infectious disease community prior to the filing of the '552 patent application in June of 2000.

14. Prior to submitting my Niacin Hypothesis to *Medical Hypotheses*, I submitted my Niacin Hypothesis to *The Lancet*. The manuscript that I submitted to *The Lancet* was the same as my Niacin Hypothesis attached hereto as **Exhibit C**. As described on its website, www.thelancet.com, *The Lancet* is an international general medical journal that will consider any original contribution that advances or illuminates medical science or practice, or that educates the journal's readers.

15. As stated on its web site, before a paper will be published it must be peer reviewed. Although *The Lancet's* web site does not give a detailed description of it review process, it is standard that a manuscript is sent out to 2 experts in the field who comment on the

accuracy, content, and importance of the manuscript.

16. A true and correct copy of *The* Lancet's peer review of my Niacin Hypothesis is attached as **Exhibit D**. *The Lancet* rejection was made in light of Brown 1991 and Tang 1996 - in fact Tang is specifically referenced.

17. One of the peer reviews stated:

> many HIV infected people take vitamin supplements and there have never been reports on any major effect on the clinical course except for vitamin A. Many individuals and researchers have ideas that vitamins may provide some clinical benefit in HIV infection but the niacin theory needs much better substantiation and of course some kind of clinical trial. Thus at this point the concept is so purely speculative...

See, Exhibit B, page 2 (emphasis supplied).

18. The other peer review was similarly skeptical. *See*, Exhibit B, page 3. The other review also noted that while Tang, et al. claimed a positive clinical outcome with niacin, Tang's study may have been due to "confounding factors" and/or the presence of the other B vitamins.

19. I have been practicing in the field of infectious diseases, retroviruses in particular, since 1991. I have kept abreast of medical literature in the field of retroviruses since 1991. When I submitted the '552 application in June of 2000, I was not aware of anyone other than myself who thought that administering niacin to patients with had a retroviral infection and did not have a dietary deficiency of niacin or tryptophan would increase levels of systemic tryptophan in any mammal, including humans. In my opinion, the expert opinions set forth in **Exhibit D** reflect the opinions of the infectious disease community in June of 2000.

20. It is puzzling to me that experts in the field could declare something speculative that Dr. Travers would declare obvious, but perhaps it has to do with some of the less explicit details which I can outline here. Recall that niacin occurs naturally in the diet as a nutrient, and it is very difficult to obtain a niacin free diet. So when Tang et al observe that patients with high verses low nutrient amounts of niacin in their diet correlate with different outcomes it is viewed scientifically as distinct from when in the '552 application examples [and subsequently in Murray et al 2001], the patients were prospectively given a dose of niacin meant specifically to exceed nutrient amounts and to act in a manner which was pharmcodynamically distinct from nutrient amounts of niacin. While Tang et al simply observes a correlation between micronutrient intake levels of niacin and then speculates that it may relate to a role for niacin in "immune function" [page 1252], the examples provided in the patent establish the unexpected finding that high doses of niacin given therapeutically to retrovirally infected patients with normal nutrient intakes results in improved tryptophan levels.

Knowledge of State of Art in June of 2000

21. Since 1991, I have been working as a physician an average of 60 hours per week. The predominant condition that I have treated since that time is retroviral infection.

22. Since 1991, I have been regularly reviewing publications related to infectious diseases. I typically have reviewed such publications on a regular basis, approximately once a week.

23. Since 1991, I have attended seminars and other informational meetings related to treating patients with retroviral infections on a regular basis, approximately eight to ten times a year.

24. I am familiar with the types of treatment that were available to patients infected with retroviruses in June of 2000.

Ability to practice the claimed invention using the '552 application as a guide.

25. I have recently reviewed the '552 application.

26. It is typical that patients with retroviral infections will periodically ask their physician to administer a "non-prescription" therapy, and physicians will then work with patients in an attempt to safely achieve the trial of therapy requested. In fact, in a recent study by Hsiao et al. over half of the retrovirally infected patients in the study were taking non-prescription therapies, and two-thirds of those patients discussed these therapies with their physicians. See Hsiao AF. et al. Complementary and Alternative Medicine Use and Substitution for Conventional Therapy by HIV infected Patients. J. Acquir Immune Defic Syndr. 2003 Jun 1; 33(2): 157-165.

27. Based upon my review, I could practice the invention using the '552 application as a guide for the following reasons:

    a. The '552 application provides information on the administration of niacin and well as cites references for the reader to learn more information about the administration and effects of niacin. In addition, medical doctors or those in the medical field are often familiar with niacin. Those who are not readily familiar with niacin know that much information can be found regarding the administration and effects of niacin on "medline", in journals, books and other commonly available resources.

    b. The '552 application tells me that the preferred method to combat plasma tryptophan depletion is to "administer niacin in 'pharmacological doses'". ('552 application, pg. 7, line 12).

    c. The '552 application recommends that I administer a dose greater than 20 milligrams per day because a lesser dose would not be expected to produce the pharmacological

effect of combating plasma tryptophan depletion. ('552 application, pg 8, line 1).

d. The '552 application informs me to expect pharmacological activity to occur at a dose of 100 milligrams per day. ('552 application, pg. 8, lines 10-11).

e. The '552 application informs me to expect that a patient will under go a reverse systemic tryptophan depletion upon the daily administration of 100 milligrams of niacin. ('552 application, pg. 8, lines 10-15).

f. The '552 application informs me that the preferred method of administration of niacin in this invention is oral administration. ('552 application, pg 9, lines 2-3).

g. The '552 application informs me that the preferred dose is 500 milligrams of niacin per day. ('552 application, pg. 9, lines 3-4).

h. The '552 application informs me that the preferred form of niacin to practice this invention is nicotinamide. ('552 application, pg. 9, lines 3-4).

i. By way of example, the '552 application informs me that administering 3 grams of nicotinamide per day for two months can be expected to increase plasma tryptophan between 20% and 80%. ('552 application, Table 3).

j. The known safe maximum dose for nicotinamide is 3 grams per day and this readily supported by the medical literature. *See, e.g.* M. Knip et al., Safety of High-Dose Nicotinamide: A Review, 43 Diabetologia 1337-1345 (2000), a copy of which is attached as **Exhibit E.**

k. The laboratory test to monitor plasma tryptophan concentrations is widely available.

l. The '552 application provides baseline systemic tryptophan levels that can be expected as well as expected increases in systemic tryptophan. ('552 application, Table 3). Furthermore, medical literature provides gives expected and target tryptophan levels. *See, e.g.*, **Exhibit B.** Werner et al came up with 91 micromol/l as a baseline for systemic tryptophan from their study on tryptophan and HIV in 1988 *See* **Exhibit B.** Other studies have come up with different normal tryptophan levels - generally lower than 91 - but Werner and colleagues have stated their normal as 91 in three different studies. *See id.* Medical literature also establishes goal levels for tryptophan [by comparing tryptophan values in patients with HIV infection to healthy control patients] make this an easily administered pharmacological agent. *See, e.g.*, **Exhibit B.**

28. As a doctor, I recognize that no two patients are the same. I also recognize that different patients react differently to the same treatment. Patients react differently to the same treatment for a myriad of reasons including different diets, different stress levels, different genetic makeup, and different metabolic rates. These observations make the determination

of optimal dosing of a drug in a particular case an individualized process.

29. If I were inclined to practice the invention disclosed in the '552 application, I would:

a. In the ordinary case, confirm both retroviral infection and tryptophan depletion with simple blood tests, and then initiate treatment for tryptophan depletion by orally administering a daily dose of nicotinamide in the preferred amount of 500 milligrams per day.

b. In a more extreme case of tryptophan depletion, I would initiate treatment by orally administering a daily dose of nicotinamide in the preferred amount of 3 grams per day.

c. In either case, I would re-assess the patient periodically. If the tryptophan levels had increased I would maintain the treatment until tryptophan level had returned to an appropriate level. If the tryptophan level had not increased, I would raise the dosage commensurate with the condition.

30. In my opinion, no additional information or experimentation is needed to practice the invention.

'552 application is not directed to "antiviral" activity but is directed to alleviating systemic tryptophan depletion

31. The invention set forth in the '552 application is not directed to antiviral therapy. The invention set forth in the '552 application is directed to treating patients with systemic tryptophan depletion. In the study disclosed in the '552 patent (the '552 study), I found no evidence that the administration of niacin had any anti-viral effect.

32. While the '552 application does not include viral measurements of the patients involved in the '552 study, the '552 study did collect some information relating to patient viral load. **Exhibit H** is a summary that I prepared of the anti-viral data obtained in the '552 study. While the data set forth in **Exhibit H** is not conclusive scientific data, this early data from patient #1 lead to the impression that nicotinamide did not have a clear in vivo antiviral effect. Even though the one-week result looked somewhat favorable at the time, it turned out to be within the daily variations seen in this test in people not on antiviral therapy when all the data was viewed as a complete set. Given the emerging data I was developing at this time on increases in plasma tryptophan, the focus of the study became the tryptophan results and further viral load measurements were not obtained on this patient or the other three patients in the patent examples. On balance, the viral measurements I obtained were inconclusive. However, the lack of meaningful decrease in viral load on the only patient measured suggests, if anything, that the administration of niacin is not a direct anti-viral therapy at all. I am not aware of any *in vivo* study that has been able to demonstrate any anti-viral effect from niacin therapy. In any event, I am not claiming that the administration

of niacin has antiviral effects.

The 3 gms/day examples can be reasonably extrapolated to cover the claims

33. The '552 application provides statistically significant human clinical data with respect to the administration of 3 gms/day of niacin. *See* '552 application, Table 3. A normal dietary intake of niacin by one infected with a retrovirus can still leads to systemic tryptophan depletion in some cases. *See, e.g.,* **Exhibit B.** Given this information, one knowledgeable in the field of infectious diseases could reasonably extrapolate the findings at 3 gms/day to a range in excess of a normal dietary intake of niacin.

34. The recommended daily dose of niacin is approximately 20 milligrams per day. *Id.* Thus, one would expect a favorable systemic tryptophan result between a range of 100 mgs/day and higher. *Id.*

The USPTO has already declared Murray et al (1995) as "non-enabled"

35. In 1995, I published two articles, both already made of record: (1) MF Murray, et al., Nicotinamide Inhibits HIV-1 in Both Acute and Chronic *In Vitro* Infection, Biochemical and Biophysical Research Communications, 210:954-959 (1995) and (2) MF Murray, et al., HIV Infection Decreases Intracellular Nicotinamide Adenine Dinucleotide [NAD], Biochemical and Biophysical Research Communications, 212:126-131 (1995). Collectively, these articles are referred to as the "1995 articles."

36. The 1995 articles were base on *in vitro* data. The same *in vitro* data that formed the basis of the 1995 articles also formed the basis of a patent application I filed with the United States Patent and Trademark Office ("USPTO"), U.S. patent application 07/906,689 (the "'689 application"). A true and correct copy of the '689 application is attached as **Exhibit F.**

37. The USPTO rejected the '689 patent application as unpatentable because it lacked *in vivo* substantiation, specifically:

> The specifications provide data only for inhibiting HIV in cells in culture. There is no data to substantial the alleged utility for treating human subjects infected with HIV. There is **no data to substantiate the alleged utility for treating human subjects infected with HIV**.... Without statistically significant data documenting the claimed method for treating patients, the person of ordinary skill in the art, knowing the unpredictability of extrapolating from in vitro results to in vivo performance, would have good reason to doubt the efficacy of applicant's invention.

See **Exhibit F,** USPTO office action, page 2-3, rejections under §101 and § 112 (emphasis supplied). A true and correct copy of the August 25, 1992 office action is also attached as **Exhibit F.**

Brown Taught Treating Tryptophan Depletion with Tryptophan – Not Niacin

38. In his 1991 paper titled "Implications of Interferon-Induced Tryptophan Catabolism in Cancer, Auto-Immune Diseases and AIDS", Dr. RR Brown discussed the implications of tryptophan metabolism to HIV and AIDS. Dr. RR Brown recognized the importance of looking for a way to therapeutically intervene with respect to systemic tryptophan depletion. At no time in his 1991 paper – or anywhere else that I have found – did Dr. Brown suggest tryptophan depletion could be treated with niacin.

39. In his 1991 paper, Dr. Brown hypothesized that decreased tryptophan might lead to decreased niacin (something that Skurnick later disproved). Dr. Brown also suggested treating tryptophan deficiency with tryptophan. Dr. Brown did not suggest niacin therapy for patients with HIV or other retroviral infections.

40. Dr. Brown's failure to suggest niacin cannot be considered a oversight since Dr. Brown is a prominent tryptophan researcher with a body of work encompassing over 100 articles stretching back to the 1950s [e.g. Brown RR, Vivian VM, Reynolds MS, et al. Some Aspects Of Tryptophan Metabolism In Human Subjects .2. Urinary Tryptophan Metabolites On A Low-Niacin Diet, J. Nutr 66 (4): 599-606 1958]

41. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

42. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Michael F. Murray 6/18/03

Michael F. Murray, M.D. Date

A

Express Mail No.: EE666389976US
Date of Deposit: June 30, 2000

Treatment Of Retrovirus Induced Derangements With Niacin Compounds

FIELD OF INVENTION

This invention relates to the treatment of mammals chronically infected with retroviruses, such as human immunodeficiency virus [HIV].

BACKGROUND

Retroviruses lead to chronic infection in mammals. Retroviruses are packets of infectious nucleic acids (i.e. genetic material) surrounded by a protective protein coat. Retroviruses are incapable of generating metabolic energy or synthesizing proteins, and thus are characterized by dependence on living cells for replication and proliferation. A retrovirus contains three enzymes: (1) reverse transcriptase, (2) protease, and (3) integrase. Current antiviral drug therapy focuses on the inhibition of reverse transcriptase and protease enzymes.

HIV is a prototypic retrovirus that causes the acquired immunodeficiency syndrome [AIDS] in humans and related primates. Worldwide, AIDS has claimed over 11 million lives. HIV currently infects more than 30 million people. Since the first reported cases of AIDS almost 20 years ago, the medical community has learned much about this retroviral disease and its diverse manifestations. A number of clinical

EXHIBIT A

manifestations of HIV infection, however, remain unexplained despite the efforts of the medical community to discover their etiology.

The Center for Disease Control and Prevention (the "CDC") has developed a "case definition" of the specific findings which, if present in a person with HIV, define AIDS. *See* Center for Disease Control and Prevention, *1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults,* MMWR Morb Mortal Wkly Rep, 41(RR-17): 1-19(1992). The CDC's case definition falls into three broad categories: (1) CD4 immune cell depletion, (2) opportunistic infections, and (3) malignancies.

In addition to the case definition of AIDS, a number of metabolic changes are associated with this chronic infection. Among them are alterations in the circulating concentrations of amino acids. Amino acids are often referred to as the building blocks of proteins. Of the common amino acids, ten amino acids are "essential." The essential amino acids are those which the body cannot synthesize and therefore must be obtained directly through the diet.

Tryptophan, an essential amino acid, is known to be depleted during HIV infection. The body utilizes dietary-derived tryptophan for several important biochemical functions, including: (1) as a building block in the synthesis of proteins, (2) as a precursor of niacin and nicotinamide adenine dinucleotide [NAD], and (3) as a precursor of serotonin. Attempting to simply replete plasma tryptophan directly through pharmacologic doses of tryptophan is not advisable given the history of patients developing "eosinophillia myalgia syndrome."

Chronic retroviral infections lead to an ongoing metabolic burden on the infected subject. This burden in HIV infection includes: (1) the turnover of CD4 cells, (2) the disturbance of lipid metabolism, (3) the depletion of serotonin, (4) the depletion of plasma tryptophan [as discussed above], and (5) the depletion of intracellular NAD. The infection, over the course of months, leads to immunodeficiency (marked by CD4 depletion) and opportunistic infections. The infection also leads to a metabolic disease state marked by a number of other manifestations, including a non-specific "wasting syndrome" and the specific disturbances and depletions previously mentioned in this paragraph.

Presently, no cure exists for HIV infection. Current treatments for HIV infected patients tend to focus on agents which inhibit two viral enzymes: the HIV-reverse transcriptase [reverse transcriptase inhibitors] or the HIV-protease [protease inhibitors]. Such agents include among others, ZDV (zidovudine), DDI (2'-3' -dideoxyinosine), and DDC (2' -3' -dideoxycytidine), each of which blocks the HIV proliferation in cells (ZDV, DDI , DDC and other such agents are referred to as the "licensed antivirals"). Unfortunately, the inhibition which occurs with the licensed antivirals is incomplete. Over time, HIV becomes resistant to the licensed antivirals. This resistance can result in a resumption of progressive immune system destruction.

Zidovudine, a licensed antiviral compound, is the only compound known to replete plasma tryptophan in HIV infected persons. However, zidovudine which is a reverse transcriptase inhibitor, causes a number of side effects including headache, nausea, and bone marrow suppression. Furthermore, HIV can develop resistance to

Zidovudine, an event which would be expected to result in recurrent tryptophan depletion.

Since HIV depletes plasma tryptophan and since this essential amino acid is required in a range of biologically necessary tasks, replenishing plasma tryptophan is essential in maintaining overall health in the HIV infected state. Although the antiviral drug zidovudine leads to an increase in plasma tryptophan in HIV infected persons, this reversal would be expected to last only so long as virus inhibition persists, and antiviral drug failure is expected with time given the incomplete nature of the drug's inhibitory effect. Niacin, as an agent to reverse infection-induced metabolic changes, works on the host side of the virus-host interaction and therefore would not be subject to the same risk of eventual viral drug resistance.

BRIEF SUMMARY OF THE INVENTION

This invention inhibits adverse metabolic and immunologic effects associated with chronic retroviral infections such as HIV by using niacin compounds, such as nicotinamide or nicotinic acid, to inhibit the depletion of tryptophan and to induce the restoration of intracellular nicotinamide nucleotides, such as nicotinamide adenine dinucleotide [NAD], in patients with retroviral infections.

More particularly, this invention relates to the oral use of pharmacologic doses of niacin compounds in persons with HIV infection in order to reverse or prevent deleterious metabolic consequences of the infection.

Another object of the invention is to inhibit adverse effects of HIV infection by combining the method of this invention with known HIV inhibitors, such as reverse transcriptase inhibitors, protease inhibitors, and others.

The invention provides a method of administering a therapeutically effective amount of niacin compounds to a patient with a chronic retroviral infection such as HIV, the etiological agent clinically associated with AIDS.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Table 1 - Baseline Characteristics of Niacin Study Patients. Illustrates the immunological status as measured by CD4 count, the concomitant use of antiviral medications, and the presence of co-infections. Niacin worked to improve tryptophan status in all four patients across this range of baseline infectious disease related findings.

Table 2 - Baseline Dietary intake of Niacin Study Patients. Illustrates the range of baseline dietary intake of tryptophan and niacin compounds. The amounts were determined by dietary recall survey, and demonstrate that tryptophan and niacin were not deficient in the baseline diet of these patients, and that the pharmacological dose of niacin used in the study was significantly higher than all participant's baseline intake.

Table 3 - Changes in plasma tryptophan levels [micromols/l] in patients taking 3 gram of nicotinamide daily for 2 months. The increase in the levels of this essential amino acid despite the unchanged dietary intake of tryptophan is consistent with decreased metabolic shunting of essential tryptophan towards niacin in HIV infected persons.

Table 4 - Changes in non-tryptophan plasma amino acid levels in HIV patients taking 3 grams/day of oral nicotinamide. The four amino acids include two essential amino acids [methionine and lysine] and two nonessential amino acids [cysteine and taurine]. In all four cases there is no discernible pattern of change with this intervention, supporting the observation that the effect of pharmacological doses of niacin on plasma tryptophan is a specific and important intervention against the metabolic disruption caused by HIV infection.

DESCRIPTION

The invention is a method for treatment of HIV infected persons with niacin administered in an amount effective to combat plasma tryptophan depletion. This invention is useful for any mammal infected with a retrovirus, including HIV. Through administration of a pharmacological dose of niacin, the retrovirus-infected subject's systemic tryptophan depletion will be reversed.

Niacin refers to either of two chemically related compounds: nicotinamide or nicotinic acid. Niacin may be administered orally, parenterally, rectally, or with any pharmaceutically accepted adjuvant or carrier. The administration and effects of niacin have undergone extensive study in the fields of diabetes and hypercholesterolemia. (*See, e.g.,* Petley A, *et al, The Pharmacokinetics of Nicotinamide in Humans and Rodents, Diabetes*, 44: 152-155 (1995); and DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). Niacin, or vitamin B3, is the common name for both nicotinic acid, i.e., C6H5N02, (pyridine-3-carboxcylic acid) or nicotinamide, i.e., C6H6ON2 (3-10 pyridinecarboxamide).

Niacin is a precursor to the biosynthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Nicotinamide nucleotides (NAD and NADP) participate in a wide array of oxidation-reduction reactions catalyzed by dehydrogenase or oxido-reductase enzymes. Virtually every aspect of cellular metabolism involves NAD/NADH or NADP/NADPH dependent reactions. In absence of sufficient supplies of nicotinamide nucleotides or niacin precursors for nicotinamide nucleotide biosynthesis, cellular functions and life itself would be impaired. (DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). The body can readily convert nicotinic acid to nicotinamide and both are expected to produce the desired therapeutic effect of combating plasma tryptophan depletion.

For this invention, it is preferred to administer niacin in "pharmacologic doses." A vitamin compound is considered a "drug," not a "nutrient," when: [1] the ingested dose exceeds the dose required for nutrient function, and [2] a pharmacologic action distinct from nutrient function is achieved. Maintaining plasma tryptophan is not a nutrient function of niacin; rather, it is a pharmacological action of niacin in retrovirally infected subjects.

All vitamins fill a nutrient function whereby a sufficient amount of the vitamin compound is required in the diet to fulfill normal metabolic needs. The body normally requires 12-18 milligrams of niacin per day to carry out the coenzyme function which defines niacin as a vitamin. The Recommended Daily Allowance [RDA] of niacin is approximately 13-20 milligrams per day. Therefore, a non-pharmacologic dose of niacin,

where niacin acts as a vitamin or nutrient compound, is approximately 20 milligrams a day or less.

The use of pharmacologic doses of niacin is distinct from the vitamin or nutrient use of niacin. (DiPalma JR and Thayer WS, *Use of Niacin as a Drug*, Annu. Rev. Nutr., 11:169-87, (1991)). Niacin's pharmacologic use can be distinguished from its non-pharmacologic (or physiologic) use by the pharmacodynamic action of the compound. Pharmacodynamic action begins when the nutrient function of niacin is complete. The maintenance of plasma tryptophan in the face of (1) retrovirus infection, and (2) normal or supernormal niacin levels is the distinct pharmacodynamic action described here.

A pharmacological dose of niacin generally occurs at a dose of about 100 milligrams per day, about 5 times the recommended daily allowance [RDA]. Niacin is safe in doses greater than 100 mg in persons with HIV, and doses of greater than 100 mg should also cause a retrovirus-infected patient to undergo a reverse systemic tryptophan depletion.

Because pharmacologic doses of niacin alleviate the drive to deplete plasma tryptophan, tryptophan depletion may represent a metabolic shunt towards niacin production. (*See* Murray, *Niacin as a Potential AIDS Preventative Factor*, Medical Hypotheses 53(5), 375-379 (November 1999), which is incorporated herein by reference.) In addition, because the essential amino acid tryptophan cannot be synthesized in the body, any agent which increases in the circulating concentrations of tryptophan in HIV infected persons presumably does so by diminishing the metabolic demands on the available supply.

The preferred embodiment of this invention is to administer a mammal infected with a retrovirus with niacin. The preferred method of administration is oral administration. The preferred dose is 500 milligrams of niacin per day in the form of nicotinamide.

The following EXAMPLE is presented to more fully illustrate the preferred embodiment of the invention. The example should not be construed to limit the scope of the invention and is to be understood merely for the purpose of illustration.

EXAMPLE - Clinical Trial of Niacin in HIV infected persons.

Four HIV infected persons participated in a trial of niacin in the form of nicotinamide. The participants were at various stages of their HIV infection as judged by their CD4 counts which ranged from 0 to 620 [see table 1]. The participants were receiving either a stable regimen of anti-viral drugs [i.e. anti-HIV drugs] for a period greater than one year or were not taking any anti-viral drugs. Two of the participants had known co-infections infections typical of HIV infected persons. Each participant took 3 grams of nicotinamide per day for 2 months. This treatment was not associated with any adverse side effects. Each participant's plasma tryptophan was measured prior to treatment and at the end of treatment [see table 3]. The average increase of plasma tryptophan of all participants was 43.9%. This change in tryptophan concentration was statistically significant with a calculated p value of p=0.0112 [using paired t-test]. The study also measured 4 other plasma amino acids which are listed in table 4. All amino acid concentrations were measured by High Performance Liquid Chromotography [HPLC]. There was no significant change in the plasma amino

acid concentrations other than tryptophan. As demonstrated in tables 3 and 4, only plasma tryptophan changed in a statistically significant manner.

The details of the invention have been set forth in the accompanying description and example above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials have been described. Other features, object, and advantages of the invention will be apparent from the description and from the claims. In the specification and the claims, the singular forms include plural referents unless the context clearly requires otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated by reference.

CLAIMS

What is claimed is:

1. A method for treating a patient infected with a retrovirus, which comprises the step of administering a daily pharmacological dose of niacin.

2. A method for treating retrovirus-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin.

3. A method for treating a patient infected with HIV, which comprises the step of administering a daily pharmacological dose of niacin.

4. A method for treating HIV-induced metabolic changes, which comprises the step of administering a daily pharmacological dose of niacin.

5. A method for treating retrovirus-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin.

6. A method for treating HIV-induced metabolic changes in a patient's systemic tryptophan levels, which comprises the step of administering a daily pharmacological dose of niacin.

7. A method for treating the depletion of tryptophan in a retrovirus-infected patient, which comprises the step of administering a daily pharmacological dose of niacin.

8. A method for treating the depletion of tryptophan in an HIV-infected patient, which comprises the step of administering a daily pharmacological dose of niacin.

9. A method for repleting nicotinamide nucleotide precursors, which comprises the step of administering a daily pharmacological dose of niacin.

10. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to prevent retrovirus-induced metabolic changes in systemic tryptophan concentrations.

11. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to slow down the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

12. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to stop the rate of retrovirus-induced metabolic changes in systemic tryptophan concentrations.

13. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is of an amount sufficient to increase a patient's level of plasma tryptophan.

14. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is greater than 100 milligrams per day.

15. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is approximately 3 grams per day.

16. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds the standard recommended daily amounts for coenzyme activity.

17. A method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds amounts normally obtainable with routine diet and supplement practices.

18. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose exceeds the RDA [recommended daily allowance] of niacin.

19. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to raise the intracellular levels of nicotinamide adenine dinucleotide [NAD] in persons with HIV infection.

20. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to replete nicotinamide nucleotide precursors [NAD].

21. A method of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose of niacin is administered to persons with HIV and other co-infections.

22. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose of niacin is administered in combination with antiviral medications such as reverse transcriptase inhibitors, and protease inhibitors.

23. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is administered in combination with other treatments for HIV infection to improve the metabolic status of an infected patient.

24. A method as in claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, where said dose is sufficient to inhibit new virus production.

ABSTRACT OF THE DISCLOSURE

Chronic infection with retroviruses, such as HIV, induce a number of metabolic derangements. The present invention relates to a method for treating retrovirus-infected subjects with niacin compounds to reverse infection induced metabolic derangements.

DRAWINGS

Table 1 - Baseline Infectious Disease Characteristics of Nicotinamide Study Patients.

Patient	CD4 count	Antiretroviral [duration]	Co-infections
1	0	none	molluscum contagiousum
2	220	PI[1]/RTI[2] [3 years]	none
3	290	RTI [2 years]	none
4	620	none	herpes zoster

Table 2 - Baseline Dietary Characteristics of Nicotinamide Study Patients. Daily intake for tryptophan and niacin by dietary survey [i.e. these numbers reflect the total non-pharmacologic amounts included in participants food and nutritional supplements.]

Patient	Tryptophan [daily intake]	Niacin [RDA%]
1	0.89 gms	42.0 mg [210%]
2	1.44 gms	22.4 mg [112%]
3	0.66 gms	32.8 mg [164%]
4	1.05 gms	24.0 mg [120%]

[1] PI is protease inhibitor.
[2] RTI is reverse transcriptase inhibitor.

Table 3 - Changes is plasma tryptophan levels [micromols/l] in patients taking 3 gram of nicotinamide daily for 2 months.

Patient	Days of Treatment	Baseline Plasma Tryptophan	Final Plasma Tryptophan	Change in Plasma Tryptophan
1.	57	31.1	52.9	+ 70.1%
2.	61	53.4	82.3	+ 54.1 %
3.	63	62.0	75.1	+ 21.1%
4.	60	51.0	66.5	+ 30.4%

Table 4 - Changes in non-tryptophan plasma amino acid levels in HIV infected patients taking 3 grams/day of oral nicotinamide.

Patient	Days of Treatment	Baseline Plasma Methionine	Final Plasma Methionine	Change in Plasma Methionine
1.	57	19.8	18.3	- 7.6%
2.	61	15.6	17.1	+ 9.6 %
3.	63	34.3	24.4	- 28.9%
4.	60	18.3	20.4	+ 11.5%

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Patient	Days of Treatment	Baseline Plasma Lysine	Final Plasma Lysine	Change in Plasma Lysine
1.	57	218.7	111.1	- 49.2%
2.	61	97.7	141.2	+ 44.5 %
3.	63	251.8	162.7	- 34.5%
4.	60	191.8	129.1	- 32.7%

Patient	Days of Treatment	Baseline Plasma Cysteine	Final Plasma Cysteine	Change in Plasma Cysteine
1.	57	48.3	54.7	+ 13.3%
2.	61	27.0	28.8	+ 6.6 %
3.	63	35.6	39.1	+ 9.8%
4.	60	75.5	61.3	-18.8%

Table 4 (cont.)

Patient	Days of Treatment	Baseline Plasma Taurine	Final Plasma Taurine	Change in Plasma Taurine
1.	57	46.3	68.8	+ 48.6%
2.	61	76.2	87.4	+ 14.4 %
3.	63	92.1	69.7	- 24.3%
4.	60	80.6	61.6	- 23.6%